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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,145	CRAVATT ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-11,13,15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,16-18 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/18/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed January 12, 2003 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-24 were pending. Applicants amended claims 12, 14 and 23. No claims were added or canceled. Therefore, claims 1-24 are still pending.

4. Claims 1-11, 13, 15 and 19 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 12, 14, 16-18 and 20-24 are examined on the merits in this action.

6. This application contains claims 1-11 drawn to a nonelected invention(s). This was addressed in the previous action (e.g., see Paper No. 19, page 2, paragraph 3). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Withdrawn Objections/Rejections

7. With respect to the rejections under the second paragraph of 35 U.S.C. 112, are withdrawn in view of Applicants' amendments to the claims and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

8. Claims 12, 14, 16-18 and 20-24 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

The present claims are directed to the use of "non-directed" R*(F-L)-X activity based probes for screening combinatorial chemical libraries wherein X is "a ligand", "L- a bond or alkylene or an alkyleneoxy chain linking group", F is "a sulfonyl group" and R is "a group of less than 1 kDal." These claims represent broad scope because they would include an infinite number of methods for producing and/or using an infinite number of structural variants (i.e., activity based probes) wherein no distinguishing structural attributes are provided for the "R" and "X" portions of the "activity based probes." The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be

connected to form the "R" and "X" portions of the "activity based probes." Furthermore, Applicants' claims include method steps for the identification of an infinite number of "active target proteins" wherein no distinguishing structural features are provided for these proteins either.

In contrast, Applicants specification is narrow in scope disclosing only **one** "non-directed" library of "activity based probes" (i.e., containing eleven members of biotinylated sulfonate esters) that was useful in identifying **one** target protein (i.e., class I aldehyde dehydrogenase, cALDH-I, was irreversibly inhibited by the sulfonate library). Here, all eleven members of the biotinylated sulfonate ester library possess the same X group (i.e., biotin), the same L group i.e., (i.e., N-(5-penylamine)-decanamido) and the same sulfonyl group (i.e., sulfonyl that has the structure $-O-S(=O)_2-$). Therefore, only the R group varies in this library. Furthermore, the R group only contains alkyl, aryl and heteroaryl groups.

With respect to adequate disclosure Applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples*, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Here, the Examiner contends that the successfully identification of one target protein (i.e., class I aldehyde dehydrogenase) via the use of one library of sulfonate esters is not "representative" of the full scope of Applicants claims. Applicants are only in possession of a method for the use of "activity based probes" wherein F = -SO3-; L = N-(5-penylamine)-decanamido; X is biotin and R represents small alkyl, aromatic and heteroaromatic groups. Furthermore, Applicants are not is possession of methods for identifying all target proteins (i.e., Applicants have only shown that they can identify a class I aldehyde dehydrogenase with this group of sulfonate esters).

The specification does not describe methods for making and/or using any specific "activity based probes" other than those mentioned above. Furthermore, Applicants successfully identified only one target protein (i.e., the class I aldehyde dehydrogenase mentioned above). The Examiner contends that there is no reason to "assume" that any other enzymes can be successfully identified in a similar fashion because Applicants have not provided any "general teachings" that would allow a person of skill in the art to extrapolate this method to other enzymes not yet tested i.e., Applicants have not shown that the method is "generalizable" (see below). Consequently, the Examiner contends that there is no teaching in the specification that would allow a person of skill in the art to determine *a priori* that applicants were in possession of the full scope of the claimed invention because Applicants have not provided any common distinguishing structural attributes that can link together *all* of the *claimed* probes and enzymes (that fall outside the narrow scope of Applicants examples).

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails

to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing a single example of a sulfonate ester library to identify a single example of a cALDH-I enzyme is insufficient to teach this broad genus. Furthermore, Applicants admit that a more "generalizable" correlation has not yet been achieved (see Adam, G. C.; Cravatt, B. F.; Sorensen, E. J. "Profiling the specific reactivity of the proteome with non-directed activity-based probes" Chemistry & Biology 2001, 8, 81-95, especially conclusion on page 91, column 1, paragraph 1, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example [i.e., Applicants make no promise that it will work for any other examples], a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. If this correlation proves generalizable [i.e., the correlation may NOT prove generalizable i.e., Applicants use the word "If"], non-directed approaches for profiling the specific reactivity of the proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings"). This underscores an inherent problem with Applicants' claimed method in that Applicants have not provided any guidance for determining what "type" of compounds to screen and under what "conditions" they should be screened (i.e., Applicants have provided no starting point for the screening) to identify the majority of target proteins that fall within the scope of the current claims, nor have they provided any assurances that the claimed method will work for other systems. The fact that the sulfonate esters proved successful in screening cALDH-I does not mean that another "sulfonyl group" (e.g., sulfates, sulfinates, sulfamates, etc.) would do the

same. Likewise, there is no guarantee that other "target proteins" (other than c-ALDH-I) will be identified using the presently claimed methods. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of examples to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

Response

9. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that they should be able to extend their ONE example (i.e., the only example that has been reduced to practice consisting of a class I aldehyde dehydrogenase, cALDH-I, which was irreversibly inhibited by an 11 membered sulfonate library, see rejection above) to an infinite number of possibilities because they have disclosed a laundry list of potential species (e.g., chemically reactive groups, active target proteins, etc.) that might work with the claimed invention. Applicants further cite *In re Bell* in support of this position noting that the representative number of species do not require the description to be of such specificity that it would provide individual support for each species that the genus embraces (e.g., see 1/12/2004 Response, pages 13-20 and references to Applicants' specification therein; see especially page 15, paragraph 4). Furthermore, Applicants state that their ONE example (i.e., one example that was reduced to practice) was not meant to be limiting.

[2] Applicants disagree with the position that there are "no distinguishing structural attributes" (e.g., see 1/12/2004 Response, page 15, paragraph 2).

[3] Applicants argue that they are entitled to claims drawn as broadly as the prior art will allow and cite Union oil Co. in support of this position (e.g., see 1/12/2004 Response, page 20, paragraph 3).

[4] Applicants argue that their invention is enabled and as a result the written description rejection should be withdrawn (e.g., see 1/12/2004 Response, page 20, last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that *In re Bell* does not apply here because the art is unpredictable. The Examiner agrees with Applicants that an "adequate description of a 'representative number' of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces" (see 1/12/2004 Response, page 20, paragraph 4; see also MPEP § 2163). However, the Examiner notes that *In re Bell* requires an "unsupported" list of species to be in a "predictable" art area (e.g., see MPEP § 2163, "in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species. Cf. *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed.Cir. 1993)"). Here, no such "genetic code" or other distinguishing feature and/or formula

(e.g., structure/function relationship) exist that would allow a person of skill in the art to conclude that Applicants were in possession of the claimed invention.

However, even if *assuming arguendo* that *In re Bell* does apply the Examiner contends that the disclosed species do not "adequately" describe the full scope of the claimed invention. Factors to be considered in determining whether there is sufficient evidence of possession include "(1) the level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention" (e.g., see MPEP § 2163). The Examiner contends (1) that the level of skill and knowledge in the art is low (see section **[3]** below), (2-3) Applicants have put forth no structural limitations or physical and/or chemical properties that would allow a person of skill in the art to narrow the number of possibilities that would need to be screened by Applicants method (e.g., see section **[2]** below), (4) the functional characteristics are NOT coupled with a known or disclosed correlation between structure and function and (5) Applicants have provided only ONE example for making activity based probes wherein F = -SO3-; L = N-(5-penylamine)-decanamido; X is biotin and R represents small alkyl, aromatic and heteroaromatic groups (see rejection above) and, as a result, Applicants list of potential species in the specification does not remedy this deficiency. Furthermore, Applicants have not provided any general methodology for synthesizing the infinite number of R(F-L)-X activity based probes that are currently claimed.

In addition, a person of skill in the art could not "immediately envision" all the different compounds that are currently claimed. The CAFC has stated, "Furthermore, disclosure of a partial structure without additional characterization of the product may not be sufficient to

evidence possession of the claimed invention. See, e.g., Amgen, 927 F.2d at 1206, 18 USPQ2d at 1021 ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.") (citations omitted). In such instances the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. Burroughs Wellcome Co. v. Barr Laboratories Inc., 40 F.3d 1223,1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention. Id." (e.g., see MPEP § 2163).

Here, the Examiner contends that NONE of the disputed species listed in Applicants specification would allow a person of skill in the art to immediately envision ANY of the R(F-L)-X activity based probes (other than the eleven-members biotinylated sulfonate ester library

disclosed in Applicants' single working example). Furthermore, Applicants have provided only a "trial and error" method of preparation of the R(F-L)-X activity based probes, which the CAFC has held does not satisfy the written description requirement (e.g., see University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 69 USPQ2d 1886 (Fed.Cir.2004)). Finally, Applicants have not disclosed any physical and/or chemical properties (e.g., structure/activity relationship) that could be used to alleviate these shortcomings.

The Examiner also contends that Applicants have failed to address the prior art of record (e.g., Adam et al.), which clearly demonstrates that Applicants were not in possession of the claimed invention (e.g., see Adam, G. C.; Cravatt, B. F.; Sorensen, E. J. "Profiling the specific reactivity of the proteome with non-directed activity-based probes" Chemistry & Biology 2001, 8, 81-95, especially conclusion on page 91, column 1, paragraph 1, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example [i.e., Applicants make no promise that it will work for any other examples], a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. If this correlation proves generalizable [i.e., the correlation may NOT prove generalizable i.e., Applicants use the word "If"], non-directed approaches for profiling the specific reactivity of the proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings"). Here, Applicants admit that they cannot "generalize" their only working example to the infinite number of possibilities that are currently claimed. Their admission clearly demonstrates that Applicants claimed scope represents a mere "wish" or "plan" which does not satisfy the written description requirement

(e.g., see *Fiers v. Revel* wherein the Court stated that an adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself").

[2] The Examiner contends that Applicants statement is wholly unsubstantiated because no rationale is provided to support this position.

[3] The Examiner contends that the prior art is in its infancy and would thus would restrict Applicants' claimed scope rather than expand it (e.g., see Adam et al. wherein Applicants admit that the art is in its infancy, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example, a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. If this correlation proves generalizable [i.e., the correlation has not been tested in the prior art and thus Applicants admit that the prior art is in its infancy], non-directed approaches for profiling the specific reactivity of the proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings").

[4] Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (*see Vas-Cath Inc. v.*

Mahurkar, 19 USPQ2d 1111, 1115). Thus, Applicants fail to overcome the written description requirement by addressing the Enablement rejection. Furthermore, the Examiner contends that Applicants are not enabled for the full scope of the invention (see below).

Accordingly, the written description rejection cited above is hereby maintained.

10. Claims 12, 14, 16-18 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for albumin-binding domain asparagine mutants, does not reasonably provide enablement for any asparagine "modified" proteinaceous ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The present claims are directed to the use of "non-directed" R*(F-L)-X activity based probes for screening combinatorial chemical libraries wherein X is "a ligand", "L- a bond or alkylene or an alkyleneoxy chain linking group", F is "a sulfonyl group" and R is "a group of less than 1 kDal." These claims represent broad scope because they would include an infinite number of methods for producing and/or using an infinite number of structural variants (i.e., activity based probes) wherein no distinguishing structural attributes are provided for the "R" and "X" portions of the "activity based probes." The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "R" and "X" portions of the "activity based probes." Furthermore, Applicants' claims include method steps for the identification of an infinite number of "active target proteins" wherein no distinguishing structural features are provided for these proteins either. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: Applicants admit that the art is inherently unpredictable (see Adam, G. C.; Cravatt, B. F.; Sorensen, E. J. "Profiling the specific reactivity of the proteome with non-directed activity-based probes" Chemistry & Biology 2001, 8, 81-95, especially conclusion on page 91, column 1, paragraph 1, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example [i.e., Applicants make no promise that it will work for any other

examples], a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. If this correlation proves generalizable [i.e., the correlation may NOT prove generalizable i.e., Applicants use the word "If"], non-directed approaches for profiling the specific reactivity of the proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings").

Therefore, the Examiner contends that the level of predictability in the art is low or absent.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants provide only one example of a "non-directed" library of "activity based probes" (i.e., containing eleven members of biotinylated sulfonate esters) that was useful in identifying one target protein (i.e., class I aldehyde dehydrogenase, cALDH-I, was irreversibly inhibited by the sulfonate library).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445

* n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response

11. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that the current claims do not read on an infinite number of methods (e.g., see 1/12/2004 Response, page 21, paragraph 3, "In contrast, it is submitted that the specification describes well-defined A activity based probes, such that skilled artisans can readily determine the probes set forth in the claims ... the specification also provides examples of particular functional groups [e.g., see pages 21-22]").

[2] Applicants disagree with the assertion that the invention cannot be extended to enzymes other than cALDH-I and argue that the Examiner has not provided any evidence in defense of this position (e.g., see 1/12/2004 Response, page 23, paragraph 1).

[3] Applicants argue that adequate guidance is provided in the specification to enable the full scope of the claimed invention and cite various passages to support this position (e.g., see 1/12/2004 Response, page 23).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants claimed invention does read on an infinite number of possibilities. In addition, the Examiner notes that nothing in Examiner statements refute this position. For example, the fact that the specification describes "well-defined" activity based probes has no bearing on the number of probes that are being set forth in the claims (i.e., you can have an infinite number of "well-defined" probes). In addition, the sheer number of R(F-L)-X probes generated by substituting the groups mentioned by Applicants citations (e..g., see 1/12/2004 Response, pages 21-22) would be astronomical because each position (e.g., R, F, L and X) can be varied independently.

[2] The Examiner contends that "evidence" has been set forth to support this position (e.g., see Adam, G. C.; Cravatt, B. F.; Sorensen, E. J. "Profiling the specific reactivity of the proteome with non-directed activity-based probes" Chemistry & Biology 2001, 8, 81-95, especially conclusion on page 91, column 1, paragraph 1, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example [i.e., Applicants make no promise that it will work for any other examples], a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. If this correlation proves generalizable [i.e., the correlation may NOT prove generalizable i.e., Applicants use the word "If"], non-directed approaches for profiling the specific reactivity of the

proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings"). Here, Applicants admit that they cannot "generalize" their only working example to the infinite number of possibilities that are currently claimed by explicitly stating that a correlation has not yet been established.

[3] The Examiner contends that page 32, paragraph 114 and the rest of the specification only provide general guidance, which is insufficient to provide adequate support in an unpredictable art area (e.g., see MPEP § 2163, "In contrast, for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession"). Here, none of Applicants cited passages provide guidance with respect to specific R(F-L)-X activity based probes in use with a specific target proteins (other than the cALDH-I example). Thus, only general lists of "potential" candidates are disclosed.

Accordingly, the Enablement rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102

12. Claims 12, 14, 16, 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Purohit et al (Purohit, A.; Williams, G. J.; Howarth, N. M.; Potter, B. V. L.; Reed, M. J. "Inactivation of Steroid Sulfatase by an Active Site-Directed Inhibitor, Estrone-3-O-Sulfamate" *Biochemistry* **1995**, *34*, 11508-11514).

For ***claims 12, 14, 16***, Purohit et al (see entire document) discloses a method for screening a library of estrones for potential inhibition of sulfatase enzymes (i.e., estrone

sulfatase and dehydroepiandrosterone sulfatase) in placental microsomes and intact MCF-7 breast cancer cells (see Purohit et al, abstract; see also figure 1, compounds 4-6), which anticipates claims 12 and 14. Here, the combinatorial chemical library has the same formula as that disclosed by Applicants wherein the X group is "estrone", the L group is a "bond", the F group is "SO_2" or alternatively "SO_2N" and the R group varies in the library to include "NH_2, NHMe and NMe_2" or alternatively "H or Me" (see Purohit et al, figure 1, compounds 4-6). Furthermore, Purohit et al discloses combining members of the library with a complex mixture (e.g., the placental microsomes and intact MCF-7 breast cancer cells that contain estrone sulfatase and dehydroepiandrosterone sulfatase) wherein conjugates are formed between the library members and the sulfatase proteins (see Purohit et al, page 11513, figure 8; see also Materials and Methods section). In addition, Purohit et al discloses isolating said conjugates from the active and inactive complex mixture (see Purohit et al, page 11509, column 2, paragraph 1). Finally, Purohit et al discloses comparing both "active" and "inactive" reaction mixtures (see Purohit et al, abstract, "The enzyme [sulfatase] is protected from inactivation by estrone sulfate [i.e., active form], which is also consistent with active site-directed inhibition. EMATE is proposed to inactivate estrone sulfatase by irreversible sulfamoylation of the enzyme [i.e., inactive form]"; see also page 11512, figure 6). Furthermore, Purohit et al discloses using two separate "portions" for the active and inactive mixture i.e., a "portion" with estrone sulfate added and a "portion" without any estrone sulfate added (see Purohit et al, page 11510, column 1, paragraph 1).

For ***claim 16***, Purohit et al discloses library members with different on-rates (see page 11510, Results, "Nature of EMATE Inhibition of Sulfatase Activity" section, especially column 2, paragraph 4).

For ***claim 20***, Purohit et al discloses R = alkyl (i.e., a methyl group) (see Purohit et al, page 11508, figure 1, compound 6).

For ***claim 21***, Purohit et al discloses F = sulfamate (see Purohit et al, page 11508, figure 1, compound 6).

Response

13. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "the present invention offers the ability to profile class of proteins in a sample on the basis of changes in protein activity rather than simply variations in protein level ... In contrast ... the methods described in Purohit are not able to differentiate a complex mixture of proteins on the basis of activity" (e.g., see 1/12/2004 Response, pages 24-25, especially page 25, middle paragraph).

This is not found persuasive for the following reasons:

The Examiner respectfully disagrees. Purohit et al. do disclose "activity" based differentiation (e.g., see above rejection, "In addition, Purohit et al discloses isolating said conjugates from the active and inactive complex mixture (see Purohit et al, page

11509, column 2, paragraph 1). Finally, Purohit et al discloses comparing both "**active**" and "**inactive**" reaction mixtures (see Purohit et al, abstract, "The enzyme [sulfatase] is protected from inactivation by estrone sulfate [i.e., active form], which is also consistent with active site-directed inhibition. EMATE is proposed to inactivate estrone sulfatase by irreversible sulfamoylation of the enzyme [i.e., inactive form]"; see also page 11512, figure 6). Furthermore, Purohit et al discloses using two separate "portions" for the active and inactive mixture i.e., a "portion" with estrone sulfate added and a "portion" without any estrone sulfate added (see Purohit et al, page 11510, column 1, paragraph 1)". Thus, Purohit et al. is able to differentiate the complex mixture on the basis of activity (e.g., see also 11510, Results, "Nature of EMATE Inhibition of Sulfatase Activity" section, especially column 2, paragraph 4 wherein library members with different "on rates" are disclosed).

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

14. Claims 12, 14, 16-18 and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gygi et al (Gygi, S. P.; Rist, B.; Gerber, S. A. Turecek, F.; Gelb, M. H.; Aebersold, R. "Quantitative analysis of complex protein mixtures using isotope-coded affinity tags" *Nature Biotechnology* **1999,** 17, 10, 994-999) and Liu et al (Liu, Y.; Patricelli, M. P.; Cravatt, B. F. "Activity-based protein profiling: The serine hydrolases" *PNAS* **1999**, 96, 26, 14694-14699) (IDS #6) and Bogyo et al (Bogyo, M.; McMaster, J. S.; Gaczynska, M.;

Tortorella, D.; Goldberg, A. L.; Ploegh, H. "Covalent modification of the active site threonine of proteasomal β subunits and the *Escherichia coli* homolog HSIV by a new class of inhibitors" *PNAS* **1996**, 94, 6629-6634).

For ***claims 12, 14, 16-18 and 20-24*** Gygi et al. disclosed a method for quantitative analysis of complex protein mixtures using isotope-coded affinity tags (ICAT) (Abstract; pg. 994, right col., 6-9). The method comprises of the following steps: (1) The side chains of cysteinyl residues in a reduced protein sample representing one cell state are derivatized with the isotopically light form of the ICAT reagent. The equivalent groups in a sample representing a second cell state are derivatized with the isotopically heavy reagent (refers to the combining step). (2) The two samples are combined and enzymatically cleaved to generate peptide fragments (refers to the sequestering step). (3) The tagged peptides are isolated by avidin affinity chromatography (refers to the determining step). (4) Finally, the isolated peptides are separated and analyzed by LC-MS/MS (electrospray ionization (ESI) MS/MS, in conjunction with microcapillary liquid chromatography (LC)) (pg. 994, right col., 12-24; figure 2) (refers to the comparing step).

The method of Gygi et al. does not expressly disclose that the probe can contain the structures disclosed by Applicants wherein F is a "sulfonyl group" and the target proteins are serine hydrolases.

The combined teachings of Liu et al and Bogyo disclosed a method of activity-based protein profiling using an active site directed probe (Abstract). The probe disclosed by Liu et al is a biotinylated fluorophosphonate, FP-biotin, (pg. 14694, left col., lines 30-33), but Bogyo et al discloses that the "sulfonyl groups" can also be used probes (see Liu

et al, page 14699, column 1, paragraph 2, "Although we have demonstrated the utility of a biotinylated fluorophosphonate as a rapid and high-sensitivity probe for detecting serine hydrolase activities directly from crude cell and tissue samples, one could envision that additional types of tagged irreversible inhibitors may succeed at labeling other classes of enzymes. For example, Bogyo and colleagues have recently used radiolabeled vinyl sulfones as selective reagents for marking members of the proteasome family of proteases (36) [wherein reference 36 refers to the Bogyo et al reference]"). The method steps of reacting protein samples (proteomic mixture) with FP-biotin (activity-based probe) include combining FP-biotin mixture with the protein samples and detecting the FP-biotin-reactive proteins by SDS/PAGE-Western Blotting (pg. 14695, right col., lines 26-64). The FP-biotin-reactive proteins are further analyzed by MALDI mass spectrometry (pg. 14696, left col., lines 11-15). FP-biotin can react with numerous serine hydrolyses (target enzyme) in crude cell and tissue samples (pg. 14698, left col., lines 1-8).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the biotinylated sulfones linked by N-(5-pentylamine)-decanamido probes as taught by the combined teachings of Liu et al and Bogyo et al in the method of Gygi et al because Bogyo et al, Gygi et al and Liu et al. disclose methods of detecting proteins from a crude cell samples (Gygi: pg. 994, right col., 6-9, and pg. 995, fig. 2; Liu: pg. 14698, left col., lines 1-8) (i.e., the references represent analogous art). One of ordinary skill in the art would have been motivated to include that the biotinylated sulfone probes and the target proteins disclosed by the combined teachings of Liu et al and Bogyo et al (e.g., serine hydrolases) in the method of Gygi et al. for the

advantage of providing a probe that is specific for profiling in a single class of proteins (Liu: pg. 14694, lines 30-33) since both Gygi et al. and Liu et al. disclose method of detecting proteins from a crude cell samples (Gygi: pg. 994, right col., 6-9, and pg. 995, fig. 2; Liu: pg. 14698, left col., lines 1-8). Furthermore, a person of skill in the art would have been motivated to combine the Bogyo et al and Liu et al references because Liu et al explicitly states that these two references should be combined (see Liu et al, page 14699, column 1, paragraph 2, "Although we have demonstrated the utility of a biotinylated fluorophosphonate as a rapid and high-sensitivity probe for detecting serine hydrolase activities directly from crude cell and tissue samples, one could envision that additional types of tagged irreversible inhibitors may succeed at labeling other classes of enzymes. For example, Bogyo and colleagues have recently used radiolabeled vinyl sulfones as selective reagents for marking members of the proteasome family of proteases (36) [wherein reference (36) refers to the Bogyo et al reference]").

Response

15. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "The present invention describes screening methods employing probes that are able to record variations in protein activity, rather than merely level of protein expressed in a cell. Gygi et al. is silent with respect to screening methods employing probes that

are able to record variations in protein activity" (e.g., see 1/12/2004 Response, page 27, paragraph 1).

[2] Applicants submit that Liu is not available as prior art since the subject matter was derived from Applicants' own work and that a declaration filed in co-pending Application No. 09/738,954 (attached herewith as Exhibit A), Liu did not contribute to the mental conception of the present invention.

This is not found persuasive for the following reasons:

[1] In response to applicant's arguments against the Gygi et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[2] The Examiner contends that the art is still available because even if Liu is removed the inventive entity would still be different (e.g., the Liu et al. publication would have Patricelli and Cravatt whereas the current application has Cravatt, Sorensen, Patricelli and Adam).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
April 4, 2004

BENNETT CELSA
PRIMARY EXAMINER